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Late Effects after Autologous Hematopoietic Cell Transplantation

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INTRODUCTION

Over 30,000 autologous hematopoietic cell transplants (HCT) have been performed yearly during the past decade. With improvement in supportive care, few patients succumb to early treatment complications; hence, more attention is being paid to causes of late complications and death. However, interpretation of the data that exist is difficult as the definition of "late" varies by study, as does the patient population, underlying diseases, HCT mobilization and conditioning regimens, stem cell sources, and duration of follow-up (Table 1). Most importantly, the methods used to estimate the incidence of late complications over time are different or are not explained in sufficient detail. Some studies report relative risk or standardized mortality compared with the general population. Other studies report an acturial estimate (which ignores competing risks and thus may overestimate the incidence), whereas others report cumulative incidence calculations.

LATE EFFECTS

In 2005, Bhatia et al. [1] reported results of the first major study directed at understanding the causes of late mortality in patients who had survived 2 or more years following transplantation. The median age at time of HCT was 36.5 years. The majority of patients received a cyclophosphamide (Cy), etoposide, total body irradiation (TBI) conditioning regimen. With a median follow-up of 7.6 years, the cohort was at a 13-fold increased risk for late death (reported as standardized mortality ratio = 13.0) when compared with the general population. The most common cause of nonrelapse mortality (NRM) was subsequent malignancies. Additional causes of late death included cardiac toxicity, pulmonary complications, and other sequela including infections. NRM was increased after carmustine and with use of peripheral blood stem cells (PBSC) as the graft source.

Researchers at the University of Minnesota studied new malignancies after HCT in 1193 children and adults [2]. The majority of patients received a TBI-based conditioning regimen. With a median follow-up of 5 years, malignancies occurred in 55 (4.6%) patients. For the entire cohort, the cumulative incidence of therapy-related myelodysplastic syndrome/acute myelogenous leukemia (t-MDS/AML) plateaued by 10 years post-HCT; in contrast, the risk of developing solid tumors continued to increased even 20 years after transplant. For t-MDS/AML, there was a trend toward a higher risk in patients who were older than 35 years at time of HCT, and the risk was higher in patients who received PBSC as their stem cell source.

Itälä et al. [3] reported late (over 100 days from HCT) complications for a cohort of 1482 adult patients. NRM was observed in 68 patients (4.6%). The most common causes of NRM were second malignancies, infections, and cardiac events. Infections occurred a median of 28 months from transplant. The risk of NRM was comparable in patients who received TBI versus chemotherapy-only-based conditioning regimens.

Several smaller studies have also contributed to our current understanding of late complications and causes of death in adult patients with lymphoma [4-6]. André et al. [4] matched each grafted patient with 3 conventionally treated controls on age, gender, clinical stage, B symptoms, and time at risk. The majority of patients received BEAM (carmustine, etoposide, cytosine arabinoside, melphalan [Mel]) conditioning for HCT. The 5-year cumulative incidence rate of second cancers was 8.9%. Solid tumors were more frequent in grafted than in control patients, although the incidence of t-MDS/AML was similar in the 2 groups. Lavoie et al. [5] reported the long-term outcome in the first 100 adult patients with Hodgkin lymphoma (HL) treated in Vancouver. All patients received Cy, carmustine, etoposide ± cisplatin conditioning. The median time to development of a second cancer

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Table 1. Late Complications after Hematopoietic Cell Transplantation

Author and Year	n	Primary Tumor(s)	Complications	Risk Factors
Bhatia et al. 2005	854	AML ALL NHL HL	t-MDS/AML (4.7%) solid tumors (2.3%) NHL (0.2%) cardiac (0.7%) pulmonary (0.6%) other (3.9%)	carmustine, PBSC
Baker et al. 2003	1193	CML AML NHL HL Neuroblastoma Breast cancer	t-MDS/AML (2.5%)age solid tumors (1.7%) PTLD (0.1%) CML (0.1%) HL (0.1%)	age >35 years, PBSC
Itälä et al. 2006	1482	NHL MM Breast cancer HL CLL	t-MDS/AML (0.8%) solid tumors (0.7%) PTLD (0.1%) infections (1.5%) cardiac (0.9%)	NR
André et al. 1998	467	HL	t-MDS/AML (1.7%) solid tumors (0.7%) NHL (0.4%)	age = 40 years PBSC
Lavoie et al. 2005	100	HL	t-MDS/AML (2%) NR solid tumors (1%) NHL (4%) endocrine (32%) infections (10%) cardiac (5%)	
Ruiz-Soto et al. 2005	439	NHL	t-MDS/AML (0.5%) solid tumors (1.4%) pulmonary (1.1%)	previous disease recurrence prior lines chemotherapy, age

ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; HCT, hematopoietic cell transplantation; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; PBSC, peripheral blood stem cells; t-MDS/AML, therapy related myelodysplastic syndrome/acute myelogenous leukemia.

was 4.2 years, with a 15-year cumulative incidence of 9%. Other late effects included endocrine abnormalities (hypogonadism and hypothyroidism), unusual infections, and cardiac disease (majority of these patients had received prior mediastinal irradiation). Ruiz-Soto and colleagues [6] reported adverse events occurring more than 30 days after HCT. Nine subsequent malignancies were diagnosed with a 3-year cumulative incidence of 3.7%. Five patients developed pulmonary fibrosis a median of 3 years following HCT. Previous disease recurrence, prior lines of chemotherapy before HCT, and increasing age were risk factors for developing a second tumor.

Majhail et al. [7] reported the prevalence of self-reported nonmalignant late effects in 276 adult survivors of autologous HCT for lymphoma. Compared to siblings, HCT survivors reported a significantly higher frequency of cataracts, dry mouth, hypothyroidism, bone impairments, congestive heart failure, exercise-induced shortness of breath, and neurosensory impairments. In a study by Choi and colleagues [8] of 562 patients, the cumulative incidence of delayed chronic kidney disease was 3.8% at 5 years, with advanced age and a primary diagnosis of multiple myeloma (MM) being risk factors.

Several studies address the long-term complications in children. The European Blood and Marrow Transplantation Acute Leukemia Working Party reported outcomes of 387 children who underwent transplantation for AML in first remission [9]. Of patients surviving at least 18 months, 33% experienced at least 1 late sequelae, including impairment of growth velocity, hypothyroidism, and hypogonadism. Common long-term complications in children with neuroblastoma following TBI + chemotherapy HCT conditioning include growth and pubertal failure, hearing impairment, orthopedic complications, renal impairment, and thyroid abnormalities [10].

In summary, the most common cause of NRM is a second malignancy, with t-MDS/AML and solid tumors being seen most frequently. The risk for t-MDS/AML appears to be highest within the first decade following HCT; in contrast, patients remain at risk of solid tumors for at least 20 years. Several reports have described an increased risk for late infectious complications. Fatal cardiac, pulmonary, and kidney disease are uncommon events. Nonfatal late effects include cataracts, hypothyroidism, and neurosensory impairments; in addition, children experience growth and developmental failure. Investigators should make

a concerted effort to present data as cumulative incidence rates to facilitate comparisons between studies.

IS THE TRANSPLANT TO BLAME?

Second malignancies

Following the initial reports of post autologous HCT t-MDS/AML in 1994, subsequent studies reported actuarial or cumulative incidences ranging from 1% to 24% (reviewed in [11]). Some investigators noted that pre-HCT abnormalities not detected by cytogenetic analysis could be detected by fluorescein in situ hybridization (FISH), lending credence to the hypothesis that pre-HCT therapy was to blame. Others noted that PBSC as the graft source and use of TBI-based preparative regimens increased the risk of t-MDS/AML.

Results from 2 prospective studies are supportive of a strong association of large, cumulative doses of alkylating agents with the development of t-MDS/AML. The German Low Grade Lymphoma Study Group reported results from a prospective trial that randomized 440 patients following alkylator-based induction therapy to autologous HCT versus interferon alpha maintenance for indolent lymphoma [12]. The 5-year cumulative incidence for secondary hematologic neoplasias after HCT was significantly higher at 3.8% compared to the interferon arm of 0.0%. Similarly, in a prospective study from Arkansas of patients transplanted for MM, all patients who developed t-MDS/AML belonged to a subgroup of patients initially treated with more than 1 cycle of an alkylator-based chemotherapy regimen, whereas those patients proceeding to transplant after only 1 cycle did not develop leukemia [13].

Several groups have reported that HCT alone is not associated with an increased risk of t-MDS/AML. Harrison et al. [14] reported a retrospective comparative study of 4576 patients with HL 595 patients had received high-dose BEAM chemotherapy with autologous HCT. They identified 3 pre-HCT risk factors for t-MDS/AML: quantity of prior therapy, exposure to MOPP (mechlorethamine, vincristine, prednisone, procarbazine), and lomustine chemotherapy. Likewise, the Vancouver group compared the incidence of second malignancies among patients with HL treated with high-dose chemotherapy conditioning and autologous HCT compared with patients who received conventional chemotherapy alone and did not see an increased risk with HCT [15]. Krishman et al. [16] used a retrospective cohort and a nested case-controlled design study to assess risk factors for t-MDS/AML in 612 HL and NHL patients. Stem cell priming with etoposide resulted in a 12.3-fold increased risk of t-MDS/AML with 11q23/21q22 abnormalities. Multivariate analysis revealed an association between prior irradiation and the risk of t-MDS/AML, but failed to reveal any associations with HCT.

The Arkansas group reported a low incidence of cytogenetically defined MDS following auto HCT for MM [17]. The 10 year estimated actuarial incidence was 1%, and was linked to a CD34 yield of less than 3×10^4/kg and need for more than 2 apheresis procedures, suggesting damage to hematopoietic stem cells that antedated HCT. Furthermore, patients who received post-HCT consolidation chemotherapy had late-onset MDS, suggesting possible post-HCT stem cell damage.

What conclusions can be drawn from these studies? Compared to the general population, it is clear that patients undergoing autologous HCT are at an increased risk of developing second cancers, and that there is a strong association with high, cumulative doses of alkylator therapy. Transplantation of collected stem cells with occult chromosomal damage from prior therapies or priming chemotherapy may lead to outgrowth post-HCT of preleukemic clones. Other factors, including TBI, have been identified as risk factors in some studies but not in others, suggesting that most likely pre-HCT therapies, priming chemotherapy, HCT conditioning regimens, post-HCT therapies as well as underlying immunologic deficiencies impairing cancer surveillance all contribute to the development of post-HCT malignancies.

Other Late Complications

In an analogous manner, other late complications of autologous HCT are most likely the culmination of numerous factors. Pretransplant comorbidities, underlying disease, pre-HCT chemo- and radiotherapy, genetics, age, life style (including smoking, alcohol use, and diet) as well as HCT and post-HCT therapies most likely all have an impact on whether or not a patient is more susceptible to infections or suffers from late organ toxicity.

MINIMIZING LATE EFFECTS

With the knowledge that the etiology of late complications post HCT is multifactorial, steps must be taken to minimize the potential for late effects when developing and implementing a therapeutic plan. Well-designed prospective trials have enabled physicians to move to transplant earlier in the course of a disease for certain high risk patients, thus limiting pre-HCT therapies. For patients with primary refractory disease who need additional salvage therapy prior to transplant, minimizing exposure to alkylating agents would be prudent if equally effective alternatives are available. Non-TBI conditioning regimens

should be considered when considered equivalent in outcomes to TBI-based regimens. Although such efforts may reduce the risks, patients will most likely continue to develop second malignancies and late complications. Children should undergo evaluation by endocrinologists familiar with the side effects of HCT on growth, puberty, and endocrine abnormalities. Likewise, transplant physicians must be cognizant of the increased risk for t-MDS/AML in the first few years and for solid tumors for over 20 years following HCT, counsel patients appropriately, and ensure ongoing follow-up. In addition to second malignancies, prudent observation and testing for infections, cardiopulmonary, and renal abnormalities in HCT recipients should be life long.

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